A Novel Diterpenoid from *Euphorbia fischeriana*

Yu-Bo Wang, Guang-Min Yao, Hong-Bing Wang, and Guo-Wei Qin*
Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 201203, P. R. China

(Received May 24, 2005; CL-050680)

Langduin D, a novel modified *ent*-abietane diterpenoid with an arylphloroglucinol moiety was isolated from the roots of *Euphorbia fischeriana*. Its structure was established by spectral data and confirmed by X-ray crystallography.

Euphorbia fischeriana Steud. (Euphorbiaceae) is a perennial herbaceous plant distributed mainly in north China. The dried plant root is commonly known as "*langdu*" in traditional Chinese medicine for the treatment of oedema, indigestion, and expectorant.[1] The most characteristic secondary metabolites of this plant are *ent*-abietane diterpenoids. For example, jolkinolides A and B exhibited significant antitumor activities against several tumor lines such as Sarcoma 180 and Ehrlich ascites in mice.[2–4] As part of fundamental research for searching biologically active compounds from the specie of *E. fischeriana*, we have isolated several new diterpenoids.[5–7] Among these compounds, langduin C, a novel symmetrical dimeric diterpenoid with a 6/6/5 ring system instead of normal 6/6/6 ring system found in *ent*-abietane skeleton. In a continuing study on minor diterpenoids from the same plant, additional novel modified *ent*-abietane diterpenoid was isolated, namely langduin D (**1**). Unlike langduin C, compound **1** consists of a modified *ent*-abietane diterpenoid and an arylphloroglucinol moiety. This paper describes the structural elucidation of langduin D.

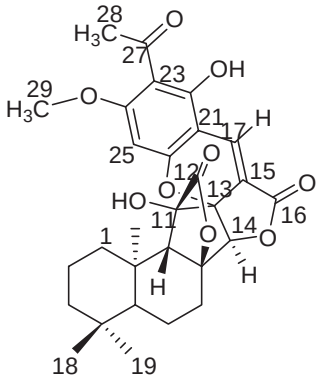


Figure 1. The structure of **1**.

Langduin D (**1**) was crystallized as yellow prism and had the molecular formula $C_{29}H_{32}O_9$ deduced by its HREIMS at m/z 524.2044, requiring 12 degrees of unsaturation. The IR spectrum exhibited absorption bands for hydroxyl and lactone groups (3448, 1774 cm^{-1}) and the UV spectrum indicated a long-range conjugated system (292 nm). The ^{13}C NMR and DEPT spectral data of **1** revealed 29 carbons consisting of five methyl, five methylenes, five methines, and fourteen quaternary carbons. The ^{1}H NMR data at δ 0.92 (3H, s), 0.95 (3H, s), 1.47 (3H, s), 2.12 (1H, s), 5.32 (1H, s), 7.82 (1H, s) and ^{13}C NMR data of compound **1**,[8] showed similarities with the monomer structure of langduin C, a modified *ent*-abietane diterpenoid, except for one acetyl methyl at δ 2.60 (3H, s), one methoxyl at δ 3.98 (3H, s), one aromatic proton at δ 6.06 (1H, s). The remained fragment $C_9H_8O_4$ together with the above spectral features indicated that **1** was consisted of a diterpenoid moiety and an acetylphloroglucinol moiety which containing one methyl ether group.

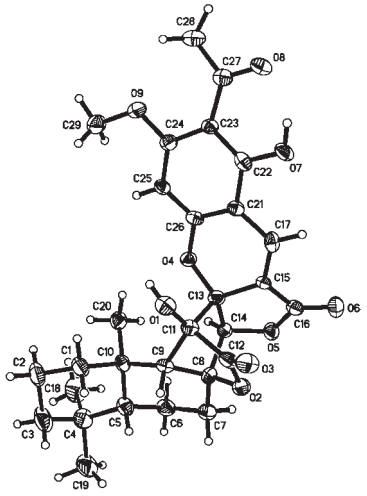
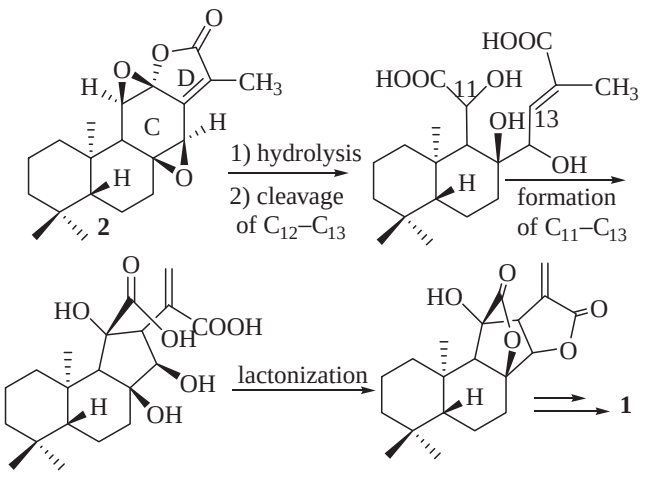


Figure 2. The ORTEP drawing of **1**.

The two structural parts in compound **1** were recognized to form an additional ring because of one degree unsaturation remained. The downfield chemical shift of C-13 (compared with langduin C) and HMBC correlations of H-17 with C-22 and C-26 and of H-25 with C-21 indicated that the two moieties were connected through linkage of C_{17}–C_{21} and C_{13}–O–C_{26}. The relative stereochemistry of **1** was deduced from NOESY spectral data while the *trans* A/B ring junction was presumed on biogentic grounds.[9] The correlations of H-20 with H-14 and of H-5 with H-9 were observed in NOESY spectrum suggesting that H-14 was α oriented and H-9 was β oriented. Compound **1** also was proposed to be a derivative from jolkinolide B (**2**) (Scheme 1), which bearing *ent*-configuration proved by chemical evidence.[10,11] The structure and the relative stereochemistry of **1** was further confirmed by X-ray crystal structure analysis.[12]

Diterpenoids are rich in natural products and contain a number of structural classes derived from variation of frameworks. Langduin D (**1**) is a rare example in natural products that a modified *ent*-abietane diterpenoid combined with an arylphloroglucinol moiety by direct carbon–carbon linkage. The modified *ent*-abietane moiety in **1** was obviously derived from jolkinolide B (**2**), a known *ent*-abietane diterpenoid isolated from the same plant, by successive oxidative cleavage of rings C and D, rearrangement and lactonization in biochemical consideration



Scheme 1. Proposed biosynthetic route of **1**.

(Scheme 1). This inter molecular transformation was occurred probably due to spatial proximity of epoxy and lactone functions in rings C and D. Up to now, this modified *ent*-abietane structure has never been found as a monomer, only as a constructing part in nature. Although compound **1** possessed an unique structure, it showed no inhibitory activity toward HIV-1 PR and HIV-1 RT in our testing according the literature methods.[13,14]

References and Notes

1 "Flora Reipublicae Popularis Sinicae," ed. by Agendea Academmiae Sinicae, Science Press, Peiking, China, (1999), Tomus 71(2), p 5.

2 G. F. Liu, S. S. Yang, Z. Q. Yang, J. A. Zhang, H. Q. Zhao, and X. M. Fan, *Zhongyao Tongbao*, **12**, 484 (1987).

3 G. F. Liu, Y. Q. Fu, Z. Q. Yang, H. Q. Zhao, and X. M. Fan, *Zhongyao Tongbao*, **13**, 291 (1988).

4 G. F. Liu, Z. Q. Yang, Y. Q. Fu, Z. G. Lou, and S. X. Wu, *Zhongcaoyao*, **20**, 290 (1989).

5 Q. G. Ma, W. Z. Liu, X. Y. Wu, T. X. Zhou, and G. W. Qin, *Phytochemistry*, **44**, 663 (1997).

6 C. T. Che, T. X. Zhou, Q. G. Ma, G. W. Qin, I. D. Williams, H. M. Wu, and Z. S. Shi, *Phytochemistry*, **52**, 117 (1999).

7 T. X. Zhou, G. H. Bao, Q. G. Ma, G. W. Qin, C. T. Che, Y. Lv, C. Wang, and Q. T. Zheng, *Tetrahedron Lett.*, **44**, 135 (2003).

8 Compound **1**: mp 251–252 °C; $[\alpha]_D^{21}$ +30° ($c = 0.115$, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 364 (4.13), 292 (4.48), 205 (4.46), 194 (4.23) nm; IR (KBr) ν_{max} 3448, 1797, 1774, 1606, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15–1.99 (m, H-1), 1.68 (m, H-2), 1.25–1.50 (m, H-3), 1.03 (d, $J = 11.1$ Hz, H-5), 1.93 (brd, $J = 8.6$ Hz, H-6), 1.79–1.52 (m, H-7), 2.12 (s, H-9), 5.32 (s, H-14), 7.82 (s, H-17), 0.92 (s, H-18), 0.95 (s, H-19), 1.47 (s, H-20), 6.06 (s, H-25), 2.60 (s, H-28), 3.98 (s, H-29); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.1 (C-1), 18.0 (C-2), 41.6 (C-3), 33.1 (C-4), 54.5 (C-5), 18.5 (C-6), 28.5 (C-7), 85.2 (C-8), 69.8 (C-9), 37.8 (C-10), 89.3 (C-11), 174.2 (C-12), 82.8 (C-13), 82.9 (C-14), 111.2 (C-15), 165.7 (C-16), 132.6 (C-17), 33.9 (C-18), 21.5 (C-19), 17.8 (C-20), 105.0 (C-21), 160.1 (C-22), 106.5 (C-23), 166.7 (C-24), 90.2 (C-25), 165.3 (C-26), 203.5 (C-27), 32.9 (C-28), 56.3 (C-29); HREIMS m/z 524.2044 $[M]^+$ (calcd for $C_{29}H_{32}O_9$, 524.2046).

9 P. M. Dewick, "Medicinal Natural Products, a Biosynthetic Approach," John Wiley & Sons Ltd., U.K. (1997), pp 189–193.

10 D. Uemura, C. Katayama, and Y. Hirata, *Tetrahedron Lett.*, **18**, 283 (1977).

11 S. Katsumura, A. Kimura, and S. Isoe, *J. Chem. Soc., Chem. Commun.*, **1983**, 330.

12 X-ray diffraction structure determination for compound **1**. Crystal data: $C_{29}H_{32}O_9 \cdot H_2O$; crystal size ($mm^3$) 0.269 × 0.208 × 0.114 yellowish prism; crytal system orthorhombic; space group $P2_1$; unit cell dimensions $a = 7.6049$ (6) Å, $b = 20.3114$ (17) Å, $c = 19.2794$ (15) Å; volume 2976.7 (4) $Å^3$; $Z = 4$; formula weight 542.56; density (calcd) 1.211 g/cm^3; absorption coefficient 0.091 mm^{-1}; $F(000) = 1152$. The reflection data were collected on a Bruker Smart Apex CCD diffractometer, using graphite-monochromated radiation Mo Kα $\lambda = 0.71073$ Å. A total of 17112 reflections were collected in the range $2.01° \leqq \theta \leqq 26.49°$ of which 11687 unique reflections with $I > 2\sigma(I)$ were used for the analysis, and were used for refinement. The final R and R_w were 0.0660 and 0.1836, respectively, with goodness-of-fit = 0.919. Crystallographic data reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 261069. Copies of the data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +044 1223 336033); or deposit@ccdc.cam.ac.uk).

13 D. Hoffmann, I. Assfalg-Machleidt, H. Nitschko, K. von der Helm, U. Koszinowski, and W. Machleidt, *Biol. Chem.*, **384**, 1109 (2003).

14 F. Odawara, H. Abe, T. Kohno, Y. Nagai-Fujii, K. Arai, S. Imamura, H. Misaki, H. Azuma, K. Ikebuchi, H. Ikeda, S. Mohan, and K. Sano, *J. Virol. Methods*, **106**, 115 (2002).

Published on the web (Advance View) July 16, 2005; DOI 10.1246/cl.2005.1160